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Parental Serotonin Transporter Polymorphism (5-HTTLPR) Moderates Associations of Stress and Child Behavior With Parenting Behavior

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The serotonin transporter-linked polymorphic region (5-HTTLPR) is associated with caregiving in nonhuman animals and with affective and cognitive correlates of human parenting, yet its association with human parenting is largely unknown. Using a well-characterized sample of parents and offspring, we evaluated the association of parental 5-HTTLPR with observed positive and negative parenting behavior, as well as its biologically plausible moderation of child-related stress and disruptive child behavior as predictors of parenting. One hundred and sixty-two parents (86% mothers) and their 6- to 9-year-old children with and without attention-deficit/hyperactivity disorder were ascertained using multiple methods including structured interviews, rating scales, and observed parent-child interaction, yielding strong measures of key constructs. Controlling for multiple youth-level (e.g., sex, 5-HTTLPR genotype, disruptive behavior) and parent-level (e.g., demographics, depression, attention-deficit/hyperactivity disorder) factors, parents with an S allele exhibited significantly less observed positive parenting than those with the LL genotype. Significant Gene × Environment interactions were also observed: Child-related stress was negatively associated with observed parental negativity among SS/SL genotype parents but not LL genotype parents; next, observed disruptive child behavior was positively associated with parental negativity for both genotypes, but the effect was strongest in SS/SL parents. These preliminary findings suggest that parental 5-HTTLPR is uniquely associated with positive and negative parenting behavior, with more specific patterns according to child-related stress and disruptive child behavior. We consider implications for future research evaluating genetic influences on parenting as well as considerations for designing and delivering parenting-based interventions.

Across diverse species, offspring survival is contingent on the experience of adequate caregiving. In humans, negative parenting behavior is a robust risk factor for poor offspring cognitive, socioemotional, and physical health outcomes (e.g., Feldman, 2007; Groh, Roisman, van Ijzendoorn, Bakermans-Kranenburg, & Fearon, 2012). Conversely, positive parenting is a replicated resilience-promoting factor across risk factors ranging from poverty to trauma (Alink, Cicchetti, Kim, & Rogosch, 2009; Kim-Cohen, Moffitt, Caspi, & Taylor, 2004). In fact, interventions that promote positive parenting and reduce negative parenting improve child outcomes (Thomas & Zimmer-Gembeck, 2007). Together with evidence from cross-fostering experiments in nonhuman animals (Champagne & Meaney, 2001) and quasi-experimental studies in humans (Klahr, McGue, Iacono, & Burt, 2011), these results suggest that individual differences in parenting behavior are likely causally related to key offspring outcomes.

Surprisingly little is known about predictors of parenting, especially relative to knowledge about predictions from parenting. Crucially, identifying predictors of parenting behavior is necessary to facilitate innovations in parenting-based interventions that promote offspring development (Luthar, Sawyer, & Brown, 2006). Individual differences in parenting behavior are influenced by contextual (e.g., family stress), parent-level (e.g., psychopathology), and child-level (e.g., behavior) factors that are salient to positive and negative parental emotions (Belsky, 1984). Moreover, affective reactivity motivates and organizes parenting behavior in humans and nonhuman animals; it is therefore integral to regulation of parenting across species (Dix, 1991;

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Maestripieri, 2011). Although biological correlates of nurturing behavior are well-characterized in other mammals (Kuroda, Tachikawa, Yoshida, Tsuneoka, & Numan, 2011), they are poorly understood in humans. Despite their heritability (Klahr & Burt, 2014; McGuire, 2003), molecular genetic studies of dimensions of human parenting behavior are rare.

Given that biological systems underlying caregiving behavior are likely to be conserved across species (Maestripieri, 2011; Rilling & Young, 2014), functional genetic variants regulating these shared biological systems are strong candidates with respect to human parenting. The 44 base-pair insertion/deletion polymorphism in the promoter region of the serotonin transporter gene (5-HTTLPR) is implicated in caregiving behavior of human and nonhuman animals. 5-HTTLPR has two functional alleles: short (S) and long (L; Heils et al., 1996). The S allele decreases expression and functionality of the serotonin transporter (5-HTT), and consequently increases serotonin (5-HT) in the synaptic cleft (Murphy & Lesch, 2008). Notably, the 5-HTTLPR ortholog is associated with maternal nurturing behavior in macaques (McCormack, Newman, Higley, Maestripieri, & Sanchez, 2009), and 5-HTT knockout mice exhibit deficient social behavior (Kalueff, Olivier, Nonkes, & Homberg, 2010). Humans with the S allele exhibit increased emotionality, stress reactivity, and neuroticism (Caspi, Hariri, Holmes, Uher, & Moffitt, 2010; Lesch et al., 1996), which are correlated with suboptimal parenting (Barrett & Fleming, 2011; Lovejoy, Graczyk, O'Hare, & Neuman, 2000). However, there is also replicated evidence that S carriers exhibit superior decision making, cognitive flexibility, and social cognition (Homberg & Lesch, 2011), which may facilitate optimal parenting (Barrett & Fleming, 2011). Several studies have examined the association of parental 5-HTTLPR with individual differences in parenting behavior directly. Whereas having an S allele predicted low sensitivity in mothers of toddlers with externalizing symptoms (Bakermans-Kranenburg & van Ijzendoorn, 2008), it predicted *high* sensitivity in mothers of infants (Mileva-Seitz et al., 2011) and in a large cohort of mothers and their toddlers followed prospectively (Cents et al., 2014). Thus, the association of 5-HTTLPR with human parenting behavior remains relatively unknown.

One potential source of this inconsistency is unmeasured Gene × Environment interactions (G × E), which complicate genetic association studies (Neiderhiser, 2001). 5-HTTLPR × environmental stress interactions have been frequently reported (Caspi et al., 2010), including meta-analytic evidence that the S allele increases risk for depression in the presence of adversity (Sharpley, Palanisamy, Glyde, Dillingham, & Agnew, 2014). 5-HTTLPR may also signal differential susceptibility (Belsky, Bakermans-Kranenburg, & van Ijzendoorn, 2007; Boyce & Ellis, 2005; van Ijzendoorn, Belsky, & Bakermans-Kranenburg, 2012), conferring sensitivity to both supportive and stressful environments. Notably, in mothers of disruptive youth (Bakermans-Kranenburg & van Ijzendoorn, 2008), a group known to experience elevated child-related stress (Neece, Green, & Baker, 2012; Theule, Wiener, Tannock, & Jenkins, 2013), S carriers exhibited less sensitivity. Yet, in a population-based sample of mothers with relatively low family-related stress, S carriers exhibited *greater* sensitivity (Cents et al., 2014). Finally, a 5-HTTLPR × interparental stress interaction revealed that relative to the LL genotype, mothers with an S allele (i.e., SS or SL) exhibited greater sensitivity and less negative parenting with low stress but less sensitivity and more negativity with elevated stress (Sturge-Apple, Cicchetti, Davies, & Suor, 2012). Consistent with prioritization of biologically plausible G × E effects (Moffitt, Caspi, & Rutter, 2005), experimental evidence in nonhuman animals and meta-analytic evidence in humans suggest that 5-HTTLPR functionally influences stress reactivity. Relative to wild type mice, 5-HTT knockout mice exhibit elevated hypothalamic-pituitary-adrenal (HPA) axis reactivity with a consistency seldom encountered in rodent behavioral genetics (Caspi et al., 2010; Murphy & Lesch, 2008). In humans, and in addition to associations with elevated threat-related amygdala activity, startle response, and sympathetic reactivity (Caspi et al., 2010; Homberg & Lesch, 2011), S allele status reliably predicts exaggerated HPA reactivity to psychosocial stress (Miller, Wankerl, Stalder, Kirschbaum, & Alexander, 2013). This converges with evidence that 5-HT fibers modulate activity at each level of the HPA axis, including direct excitatory effects on hypothalamic neurons that release corticotropin-releasing factor to initiate the HPA stress response (Contesse et al., 2000). That 5-HTTLPR functionally modifies stress response implies a *biological interaction* rather than simply a statistical interaction. Thus, interactive 5-HTTLPR × stress effects on human psychosocial functioning may extend to parenting behavior and may underlie inconsistent associations between 5-HTTLPR and parenting.

Child characteristics also affect individual differences in parenting behavior, both directly and within the context of genetic influences. Despite replicated evidence that disruptive child behavior predicts parenting more robustly than the reverse (Hipwell et al., 2008; Kiff, Lengua, & Zalewski, 2011), previous studies of 5-HTTLPR and parenting have ignored these child effects. Potential evocative gene–environment correlation (rGE) is similarly ignored (see Cents et al., 2014, for a key exception), despite meta-analytic evidence that child genotypes, including 5-HTTLPR, elicit parenting via genetically influenced child characteristics (Avinun & Knafo, 2014; Pener-Tessler et al., 2013). rGE also complicates definitive inferences of G × E (Jaffee & Price, 2007). Finally, child characteristics may also *interact* with parental genotypes to predict parenting. Although parental dopamine genotypes moderated the association of disruptive child behavior with parenting (Lee et al., 2008), no study has examined similar interactions with parental 5-HTTLPR. Interaction with difficult children induced exaggerated maternal HPA response (Martorell & Bugental, 2006), which in turn is affected by 5-HTTLPR (Miller et al., 2013), suggesting biological plausibility. Thus, rigorous prosecution of

the association of parental 5-HTTLPR with parenting requires control of child 5-HTTLPR (to combat evocative rGE) and control of disruptive child behavior (to combat child effects), as well as evaluation of potential 5-HTTLPR × disruptive child behavior interactions.

Although parental 5-HTTLPR is implicated in individual differences in human parenting and its moderation of parenting predictions from parental stress and disruptive child behavior is plausible, previous studies are limited by several issues. First, parenting behavior is multidimensional, necessitating proper differentiation (e.g., positive *and* negative). Second, child-related stress is more strongly related to parenting behavior than other stress dimensions (Abidin, 1992; Deater-Deckard, 1998), but previous studies typically employ single-source self-report approaches without isolation of specific types of stress. Finally, parental depression and attention-deficit/hyperactivity disorder (ADHD) predict suboptimal parenting behavior (Chronis-Tuscano et al., 2008; Lovejoy et al., 2000). To improve the specificity of observed associations, parent psychopathology must be considered. The present study addressed these limitations directly with three key aims: (a) to test the association of parental 5-HTTLPR with positive and negative parenting behavior, with control of key parenting and genotype correlates; (b) to evaluate moderation by 5-HTTLPR of the association of multi-method measures of child-related stress with parenting behavior; and (c) to explore interactions of 5-HTTLPR with multi-method measures of disruptive child behavior in predictions of parenting. Given the small literature on 5-HTTLPR and parenting behavior, no directional hypotheses were proposed.

METHODS

Participants

Participants were 162 parents (85.8% mothers; *M* age = 41.3, *SD* = 6.5) and their 6- to 9-year-old offspring (32.7% female). Families were sampled to include children with (n = 76) and without (n = 86) ADHD. There were no significant differences between ADHD and non-ADHD groups regarding gender, ethnicity, or age ($p > .14$ for all tests). Families were recruited from a large metropolitan city in California via advertisements at local schools and pediatric offices, and via referrals from mental health providers. Parents and children were required to be fluent in English and to live together at least half of the time. Children with other disorders (e.g., depression) were included in the non-ADHD group to enhance external validity. Families were excluded if their child had an IQ less than 70 or a seizure or neurological disorder that prevented full study participation.

Procedures

Initial study eligibility was determined during a telephone screening. Eligible families (n = 230) were mailed rating scales to be completed by the primary caregiver, defined as the parent who spends the most time with the child. The primary caregiver then attended an in-person visit to our laboratory with his or her child; only the primary caregiver provided parent data. Because mothers and fathers did not differ with respect to positive ($Z = .66$, $p = .51$) and negative ($Z = .15$, $p = .88$) parenting, parenting data were collapsed across genders. After parents and children gave consent and assent, respectively, parents completed multi-method measures of parent and child functioning while children were intensively ascertained in a separate room. Parents and children also completed a valid parent–child interaction task that was videotaped for later coding of parenting and disruptive child behaviors. Of the parents, 162 had complete genetic and parenting data (Table 1). All procedures were approved by the Institutional Review Board.

Measures

Genotype. Parent and child DNA was extracted from saliva using DNA Genotek Oragene Self-Collection Kits (DNA Genotek, Inc., Ottawa, Canada). The 44 base-pair insertion/deletion polymorphism in the promoter region of 5-HTTLPR was genotyped with standard primers, producing fragments of either 484 or 528 base-pair (Heils et al., 1996). The L_G allele was not genotyped. Parent genotype frequencies were distributed in our sample as follows: SS (24.1%, n = 39), SL (45.7%, n = 74), and LL (30.2%, n = 49). These frequencies did not deviate from Hardy-Weinberg equilibrium, $\chi^2(1) = 1.11$, $p = .29$.

Parenting behavior. We used the Dyadic Parent Child Interaction Coding System (DPICS; Eyberg, Nelson, Duke, & Boggs, 2005) to assess positive and negative parenting behavior. Consisting of a valid parent–child interaction task lasting approximately 20 minutes, parents were asked to first play along with their child during an activity of the child's choosing (e.g., drawing, playing with toy); they were then asked to select a new activity and have the child play along according to parental rules; finally, parents instructed the child to clean up the toys without assistance. Counts of discrete parent behaviors were coded continuously, and two composite categories of parenting—praise and negativity—were created (Chronis et al., 2007; Chronis-Tuscano et al., 2008; Eyberg et al., 2001). Parental praise was counted when parents positively appraised their child's behavior, attributes, or actions. Parental negativity was counted when parents issued hostile or critical comments, negative commands, or sarcastic and condescending remarks. We totaled the counts of observed behaviors across each category and corrected for slight variations in the total minutes that were coded in all statistical analyses.

Interactions were coded by intensively trained research assistants. Training consisted of a full day of instruction

TABLE 1
Sample Demographics and Descriptive Statistics

	% of Sample		% of Sample or M (SD), Range
Parent gender (female)	85.8	Child 5-HTTLPR	
Parent race-ethnicity		SS	25.3
Caucasian	62.6	SL	44.8
African American	8.4	LL	29.9
Hispanic	14.8	Parental depression	6.39 (5.70), 0–29
Asian	7.1	Parental ADHD	25.17 (12.74),0–68
Mixed	7.1	Child-related stress	2.32 (0.61), 1.0–3.5
Parental 5-HTTLPR		Parenting distress	32.85 (8.20), 19–60
SS	24.1	Observed noncompliance	0.17 (0.21), 0–0.98[a]
SL	45.7	DISC ADHD/ODD	10.33 (7.09), 0–26
LL	30.2	Parental praise	11.82 (10.00), 0–64
Child gender (female)	32.7	Parental negativity	9.38 (9.13), 0–57

Note: 5-HTTLPR = serotonin transporter-linked polymorphic region; ADHD = attention-deficit/hyperactivity disorder; DISC ADHD/ODD = total number of child ADHD and oppositional defiant disorder symptoms from the Diagnostic Interview Schedule for Children.

[a]Values reflect the mean, standard deviation, and range calculated on the number of counts divided by the total minutes coded for that participant.

followed by a 2-month practice period with weekly reviews, quizzes, and coding meetings to resolve disagreements and ensure ongoing reliability. Estimations of composite category reliability were established via random selection of 20% of cases to be coded by two separate raters; the intraclass correlations in the sample were .75 (negativity) and .88 (praise). The DPICS composite categories have demonstrated strong test–retest reliability (Chronis-Tuscano et al., 2008) and predictive validity (Chronis et al., 2007), and discriminated between treatment and control families in intervention research (Robinson & Eyberg, 1981). For additional details regarding coding and psychometrics, see Li and Lee (2013).

Child-related stress. We assessed child-related stress with the UCLA Life Stress Interview (LSI; Hammen et al., 1987). The LSI is a semistructured clinician-administered interview of parents that evaluates chronic stressors in multiple domains (i.e., marital and parent–child relations, finances, work, health). We utilized the parent–child relationship domain, a measure of ongoing, typical conditions in the parent's relationship with the child over the past 6 months. Interviewers assigned scores for each domain on a scale of 1 (*exceptionally positive conditions*) to 5 (*exceptionally poor conditions*), including half points, using behaviorally specific anchors for each value. The child-related domain has demonstrated 12-month stability in clinical and community samples, as well as convergent validity with offspring reports of parental warmth and hostility (Hammen, Kim, Eberhart, & Brennan, 2009). The intraclass correlation for the LSI in our sample was .92.

We also administered the Parenting Stress Index–Short Form (PSI; Abidin, 1995). The 12-item Parental Distress subscale assesses stress associated with one's role as a parent and has demonstrated good reliability and validity (Abidin, 1995). Items were rated on a 5-point scale and a total parenting distress score was summed (α = .86), with higher scores indicating increased parenting distress. Whereas the LSI was designed to elicit behavioral descriptions of the parent–child relationship, the PSI captures the subjective experience of parenting and associated distress level (e.g., "I feel trapped by my responsibilities as a parent"). Thus, child-related stress from the LSI and parenting distress from the PSI may reflect the parent's environmental conditions and subjective distress regarding their child, respectively.

Disruptive child behavior. Disruptive child behavior was first estimated from observed child noncompliance from the DPICS just described. Child noncompliance was counted when the child refused or ignored parental commands and questions. We totaled the counts of observed noncompliance behaviors (Chronis et al., 2007; Chronis-Tuscano et al., 2008; Eyberg et al., 2001). Interrater reliability for observed noncompliance in our sample was .78.

We also estimated disruptive child behavior using the number of ADHD and oppositional defiant disorder (ODD) symptoms from the computerized Diagnostic Interview Schedule for Children–IV (Shaffer, Fisher, Lucas, Dulcan, & Schwab-Stone, 2000), a structured diagnostic interview completed with the parent; it has been extensively validated and demonstrates excellent psychometrics, including test–retest reliability and internal consistency (Shaffer et al., 2000). To reduce the number of statistical tests (thereby reducing Type I error) and given their covariation in our

sample (r = .58, p < .001), we used the sum of the total number of ADHD and ODD symptoms. Moreover, ADHD and ODD may reflect a single externalizing behavior factor with common genetic influences (Tuvblad, Zheng, Raine, & Baker, 2009).

Parent psychopathology. Parental depression was assessed with the Beck Depression Inventory-II (Beck, Steer, & Brown, 1996), a 21-item self-report measure of depression symptomatology with excellent psychometric properties. Parents rated the severity of their symptoms over the past 2 weeks on a 4-point scale and a total score was summed (α = .85). Parental ADHD was self-reported via the 18-item Adult ADHD Self-Report Scale (Kessler et al., 2005). Items consisted of a 5-point scale and a total score was summed (α = .94). The Adult ADHD Self-Report Scale has excellent reliability and validity (Adler et al., 2006).

Statistical Analyses

As with previous studies of parental 5-HTTLPR and parenting behavior (i.e., Cents et al., 2014; Mileva-Seitz et al., 2011; Sturge-Apple et al., 2012), we compared parents with at least one copy of the S allele (i.e., SS/SL; 69.8%, n = 113) to those without the S allele (i.e., LL; 30.2%, n = 49). Parental genotype was coded 0 = SS/SL, 1 = LL; both measures of child-related stress (i.e., child-related stress from the LSI, parenting distress from the PSI) and both measures of disruptive child behavior (i.e., observed noncompliance, Diagnostic Interview Schedule for Children–IV, ADHD/ODD symptoms) were entered as continuous predictors and centered to avoid scaling artifacts. Of the 162 parents with complete genetic and parenting behavior data, those with complete data on the remaining key constructs ranged from 117 to 162. Missing data were unrelated to each of the key study variables (p > .08 for all tests), suggesting that missing data were not systematic.

Given that parenting behavior consisted of overdispersed count data without excessive zero values, we fit general linear models specifying a negative binomial distribution. Thus, all reported B values are unstandardized logits. We constructed separate models predicting parental praise and negativity as follows: First, controlling for child-level (i.e., sex, 5-HTTLPR, ADHD/ODD symptoms) and parent-level (i.e., sex, race-ethnicity, depression, and ADHD) covariates, we evaluated the independent associations of parental 5-HTTLPR and child-related stress with positive and negative parenting behavior, followed by their interaction. Second, we reproduced this identical data analytic strategy but child-related stress from the LSI was replaced by parenting distress from the PSI. Third, controlling for child-level (i.e., sex, 5-HTTLPR) and parent-level (i.e., sex, race-ethnicity, depression and ADHD) covariates, we evaluated the independent associations of parental 5-HTTLPR and observed child noncompliance with parenting behavior, followed by their interaction; fourth, we reproduced this identical data analytic strategy but observed noncompliance was replaced by child ADHD/ODD symptoms. No covariates were dropped from any models just described. Simple effects analyses were conducted following significant interactions and plotted graphically. Finally, recent advances in G × E research suggest that potential confounds should be counteracted by inclusion of the covariate as well as the covariate × genotype and covariate × environment interaction terms (Keller, 2014). We therefore additionally evaluated significant G × E using this method, but given the modest sample size and to preserve statistical power, we selected a subset of the covariates for these analyses: parent ethnicity and child genotype, given our desire to prioritize control of population stratification and evocative rGE, and parental ADHD and disruptive child behavior, given that ADHD families were oversampled in the study.

RESULTS

Gene–Environment Correlation and Population Stratification

Bivariate associations among the study variables are summarized in Table 2. Parental 5-HTTLPR was unrelated to child-related stress, parenting distress, child ADHD/ODD symptoms, and observed noncompliance. Thus, passive rGE was not indicated. As just noted, to combat evocative rGE, we controlled for child 5-HTTLPR in all models.

Racial-ethnic differences in allele frequencies (Nakamura, Ueno, Sano, & Tanabe, 2000) may threaten internal validity; however, population stratification is primarily a concern when samples consist of highly distinct strata (Hutchison, Stallings, McGeary, & Bryan, 2004), unlike the current study. Nevertheless, given that population stratification is contingent upon race-ethnicity being associated with both genotype and outcome variable (Hutchison et al., 2004) and because parental 5-HTTLPR genotypes were nonrandomly distributed by race-ethnicity in our sample, $\chi^2(4) = 12.16$, p = .01, race-ethnicity was controlled in all models.

Association of Parental 5-HTTLPR with Observed Positive and Negative Parenting

Controlling for child-level (i.e., sex, 5-HTTLPR genotype, ADHD/ODD symptoms) and parent-level (i.e., sex, race-ethnicity, depression and ADHD symptoms, child-related stress) constructs, SS/SL parents exhibited significantly less praise than parents with the LL genotype (B = –.62, SE = .19, p < .01; Table 3). To confirm that this association was robust to inclusion of all environmental variables, parenting distress

TABLE 2
Bivariate Associations Among the Key Constructs

	1.	2.	3.	4.	5.	6.	7.	8.	9.
1. Parental 5-HTTLPR	—								
2. Child 5-HTTLPR	.50***	—							
3. Child-related stress	−.02	−.06	—						
4. Parenting distress	.05	.06	.38***	—					
5. Observed noncompliance	.04	.19*	−.07	.01	—				
6. DISC ADHD/ODD	.07	.03	.15	.27***	.17*	—			
7. Parental depression	−.01	.01	.19	.63***	.06	.15	—		
8. Parental ADHD	.11	.18*	.06	.40***	.04	.39***	.46***	—	
9. Parental praise	.13	−.03	−.17	.01	−.01	.12	−.01	.11	—
10. Parental negativity	.09	.15	−.13	−.12	.47***	.14	.05	.05	−.03

Note: 5-HTTLPR = serotonin transporter-linked polymorphic region genotype; DISC ADHD/ODD = total number of child attention-deficit/hyperactivity disorder and oppositional defiant disorder symptoms from the Diagnostic Interview Schedule for Children.

*$p < .05$. ***$p < .001$.

and observed noncompliance were added to the model, and parental 5-HTTLPR remained significant ($B = –.71$, $SE = .19$, $p < .001$). However, controlling for the same parent- and child-level constructs, parental 5-HTTLPR was unrelated to parental negativity ($B = .24$, $SE = .25$, $p = .34$; Table 3).

5-HTTLPR × Child-Related Stress Interactions: Predictions of Observed Parenting

To review, we tested whether parental 5-HTTLPR × child-related stress (measured separately with child-related stress from the LSI and parenting distress from the PSI) interactions were associated with observed positive and negative parenting behavior. Controlling for child-level (i.e., sex, 5-HTTLPR genotype, ADHD/ODD symptoms) and parent-level (i.e., sex, race-ethnicity, depression and ADHD symptoms) constructs, neither the parental 5-HTTLPR × child-related stress interaction ($B = .41$, $SE = .33$, $p = .21$; Table 3) nor the 5-HTTLPR × parenting distress interaction ($B < .01$, $SE = .02$, $p = .99$) was related to parental praise. Although the 5-HTTLPR × parenting distress interaction was also unrelated to parental negativity ($B = –.03$, $SE = .02$, $p = .15$), the 5-HTTLPR × child-related stress interaction significantly predicted parental negativity ($B = –.62$, $SE = .26$, $p = .02$; Table 3). Crucially, even when select covariates (i.e., parent race-ethnicity and ADHD plus child 5-HTTLPR and ADHD/ODD) were each included as a main effect, covariate × genotype term, and covariate × environmental condition term

TABLE 3
Parental 5-HTTLPR Predicts Parental Praise, Whereas a Parental 5-HTTLPR × Child-Related Stress Interaction Predicts Parental Negativity

	Parental Praise				*Parental Negativity*			
Independent Variable	*B*	*SE*	*p*	*95% CI*	*B*	*SE*	*p*	*95% CI*
Model 1								
Child gender (female)	.05	.18	.78	—	−.17	.18	.34	—
Child 5-HTTLPR (SS/SL)	.53	.21	.01*	[0.13, 0.93]	−.29	.28	.30	—
DISC ADHD/ODD	.01	.01	.55	—	.01	.01	.35	—
Parent gender (female)	−.12	.24	.61	—	.05	.22	.82	—
Parent R/E (Caucasian)	.56	.27	.04*	[0.03, 1.09]	.23	.25	.37	—
Parent R/E (African American)	−.12	.41	.77	—	.99	.39	< .01*	[0.22, 1.77]
Parent R/E (Hispanic)	.24	.33	.47	—	.96	.28	< .01**	[0.42, 1.51]
Parent R/E (Asian)	−.03	.34	.94	—	.27	.41	.51	—
Parental ADHD	.01	.01	.42	—	.01	.01	.85	—
Parental depression	−.03	.02	.06	—	.01	.02	.95	—
Child-related stress	−.04	.13	.78	—	−.18	.14	.19	—
Parental 5-HTTLPR (SS/SL)	−.62	.19	< .01**	[–0.99, –0.25]	.24	.25	.34	—
Model 2								
All IVs from Model 1 included	—	—	—	—	—	—	—	—
5-HTTLPR × Child-related stress	.41	.33	.21	—	−.62	.27	.02*	[–1.14, –0.09]

Note: 5-HTTLPR = serotonin transporter-linked polymorphic region; CI = confidence interval; DISC ADHD/ODD = total number of child attention-deficit/hyperactivity disorder and oppositional defiant disorder symptoms; R/E = race-ethnicity; IV = independent variable.

*$p < .05$. **$p < .01$.

per Keller (2014), the parental 5-HTTLPR × child-related stress interaction remained significantly associated with parental negativity (B = –.99, SE = .45, p = .02). Additionally, when the covariates were similarly included, the parental 5-HTTLPR × parenting distress interaction for parental negativity was significant (B = –.09, SE = .02, p < .001), and was directionally consistent with the 5-HTLLPR × child-related stress interaction.

Post hoc analyses of the parental 5-HTTLPR × child-related stress interaction (Figure 1) indicated that the simple slope for child-related stress for the SS/SL genotype, but not the LL genotype, differed significantly from zero (B = –3.80, SE = 1.85, p = .04; and B = 2.25, SE = 1.99, p = .26, respectively). That is, child-related stress was negatively associated with parental negativity for SS/SL parents only. Parental negativity differed significantly between the SS/SL and LL parents at child-related stress scores below 2.02 (B = 4.28, SE = 2.19, p = .05).

5-HTTLPR × Disruptive Child Behavior Interactions: Predictions of Observed Parenting

Controlling for the main effects of child-level (i.e., sex, 5-HTTLPR genotype) and parent-level (i.e., sex, race-ethnicity, depression and ADHD symptoms) covariates, neither the parental 5-HTTLPR × observed child noncompliance (B = .31, SE = .65, p = .63) nor the 5-HTTLPR × child ADHD/ODD symptoms interactions (B = -.01, SE = .02, p = .62) predicted parental praise. Next, the parental 5-HTTLPR × ADHD/ODD interaction was unrelated to parental negativity (B = .01, SE = .02, p = .60), but the parental 5-HTTLPR × observed child noncompliance interaction significantly predicted parental negativity (B = 1.05, SE = .57, p = .02; Table 4). Finally, this interaction was robust to the stringent G × E criteria outlined by Keller (2014) based on statistical control of parent ethnicity and ADHD as well as child 5-HTTLPR (B = 1.64, SE = .60, p < .01).

TABLE 4
Parental 5-HTTLPR × Observed Child Noncompliance Interaction Predicts Parental Negativity

Independent Variable	*B*	*SE*	*p*	*95% CI*
Model 1				
Child gender (female)	.02	.15	.89	—
Child 5-HTTLPR (SS/SL)	.10	.19	.59	—
Parent gender (female)	−.09	.19	.62	—
Parent R/E (Caucasian)	.03	.20	.88	—
Parent R/E (African American)	.84	.37	.02*	[0.22, 1.67]
Parent R/E (Hispanic)	.54	.22	.01*	[0.16, 1.01]
Parent R/E (Asian)	−.17	.35	.62	—
Parental ADHD	.01	.01	.24	—
Parental depression	−.01	.01	.91	—
Observed noncompliance	1.65	.24	< .01***	[0.19, 1.60]
Parental 5-HTTLPR (SS/SL)	.03	.19	.87	—
Model 2				
All IVs from Model 1 included	—	—	—	—
5-HTTLPR × Observed noncompliance	1.05	.47	.02*	[0.13, 1.98]

Note: 5-HTTLPR = serotonin transporter-linked polymorphic region; CI = confidence interval; R/E = race-ethnicity; ADHD = attention-deficit/hyperactivity disorder; IV = independent variable.
*p < .05. ***p < .001.

Post hoc analyses of the significant parental 5-HTTLPR × observed noncompliance interaction (Figure 2) indicated that the simple slope for observed noncompliance for the SS/SL and LL genotypes both differed significantly from zero (B = 19.88, SE = 3.54, p < .001; and B = 8.19, SE = 3.27, p = .01, respectively). That is, the positive association of observed noncompliance with parental negativity was evident for both genotype groups, but it was strongest for SS/SL

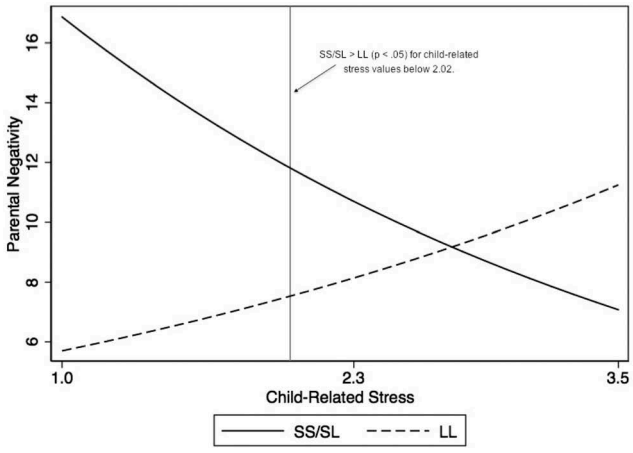

FIGURE 1 Parental 5-HTTLPR × child-related stress interaction predicting parental negativity. *Note*: The axes are scaled according to raw values to aid interpretation, but the plotted data are taken directly from analyses with mean-centered variables.

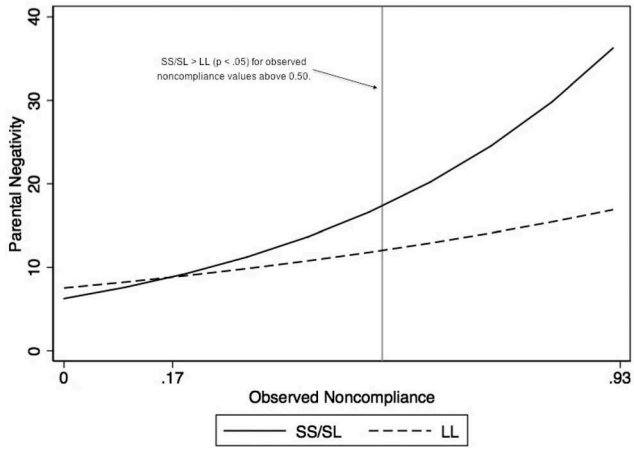

FIGURE 2 Parental 5-HTTLPR × observed child noncompliance interaction predicting parental negativity. *Note*: The axes are scaled according to raw values to aid interpretation, but the plotted data are taken directly from analyses with mean-centered variables.

parents. Parental negativity differed significantly between the SS/SL parents and the LL parents at observed noncompliance scores above 0.50 ($B = 5.30$, $SE = 2.71$, $p = .05$).

DISCUSSION

This study tested the association of parental 5-HTTLPR with observed positive and negative parenting behavior, as well as its separate interactions with child-related stress and disruptive child behavior. In a well-characterized sample of parents and their 6- to 9-year-old offspring with and without ADHD, parental 5-HTTLPR uniquely predicted observed parental praise, even with stringent control of multiple child-level (i.e., sex, 5-HTTLPR, disruptive behavior) and parent-level (i.e., sex, race-ethnicity, depression, ADHD, child-related stress) correlates. Parents with an S allele exhibited less praise than parents with the LL genotype, but parental 5-HTTLPR was unrelated to observed negativity. Interactions were also observed: (a) Child-related stress was negatively associated with parental negativity for the SS/SL, but not LL, parents; and (b) observed child noncompliance was positively associated with parental negativity, and this association was stronger for SS/SL than LL parents. These findings reflect novel, preliminary evidence that parental 5-HTTLPR is uniquely associated with positive and negative parenting, with more specific patterns based on child-related stress and child noncompliance.

We observed that the S allele predicted *less praise* than the LL genotype, albeit in both mothers and fathers, similar to evidence that SS mothers were *less sensitive* with their 2-year-olds than SL/LL mothers (Bakermans-Kranenburg & van Ijzendoorn, 2008). However, SS/SL mothers exhibited *greater sensitivity* with their 14-month-old children longitudinally (Cents et al., 2014), and cross-sectionally with their infants (Mileva-Seitz et al., 2011). Despite their positive association (Johnston, Murray, Hinshaw, Pelham, & Hoza, 2002), parental praise and sensitivity are separable constructs (Johnston et al., 2002; Tamis-LeMonda, Shannon, Cabrera, & Lamb, 2004). We also contend that developmental influences are salient. The present study was based on parents of children 6 to 9 years of age, whereas previous studies included mothers of very young children. Given evidence that positive parenting changes prospectively (Haskett, Neupert, & Okado, 2014), adaptive parenting manifests differently across development. For example, despite its centrality to effective parenting of adolescents, parental monitoring is less relevant during childhood (Frick, Christian, & Wootton, 1999). Given the relative infancy of this literature, future research on 5-HTTLPR and parenting should extend across offspring development and further examine separable parenting behavior dimensions (e.g., praise *and* sensitivity).

Although the S allele may confer differential susceptibility (van Ijzendoorn et al., 2012), SS/SL parents in the current study exhibited significantly *higher* parental negativity than LL parents specifically under *low* child-related stress, which may partly reflect the narrow range of child-related stress observed in this sample. In addition, the rs25531 A > G substitution results in two functional L allele variants: L_A and L_G. L_G is similar to the S allele in expression and binding potential, and therefore can alter 5-HTTLPR functionality (including potential differential effects by race; Praschak-Rieder et al., 2007). Thus, given that L_G was not genotyped, we cannot rule out this potential effect. Alternatively, the association of the S allele with negative affectivity (Lesch et al., 1996) suggests that trait-level negative affect may contribute to the elevated parental negativity observed for the SS/SL genotypes at *lower* levels of stress. In addition, child-related stress was inversely associated with parental negativity for the SS/SL, but not LL, genotype. Meta-analytic evidence suggests that S allele carriers exhibit exaggerated stress reactivity and emotionality with environmental stress (Miller et al., 2013), including depression (Sharpley et al., 2014) that predicts parental withdrawal and disengagement (Goodman & Brand, 2009; Lovejoy et al., 2000). Thus, low parental negativity among SS/SL parents under *higher* child-related stress may reflect adversity-driven vulnerability to socially withdrawn behavior. Whereas explicit negative parenting (e.g., harsh verbalizations) is more sensitive to concurrent depression, withdrawn/disengaged parenting is sensitive to concurrent depression *and* depression vulnerability (Lovejoy et al., 2000). Although we controlled for parental psychopathology, parents in this study were only modestly depressed, and therefore SS/SL parents were perhaps prone to social withdrawal under elevated stress rather than explicit negative parenting. Moreover, that parents were less verbally expressive as child-related stress increased converges with our finding that SS/SL parents exhibited less praise than LL parents overall. Thus, future studies must identify mediators of interactive 5-HTTLPR × stress effects on parenting and evaluate parental affect and verbal expression as temporally ordered mediators.

Parental 5-HTTLPR also significantly moderated predictions of parental negativity from observed child noncompliance. These results are broadly suggestive of differential susceptibility given that SS/SL parents were more negative than LL parents in the presence of elevated child noncompliance and simultaneously less negative than LL parents at low levels of noncompliance. Moreover, observed noncompliance was more strongly associated with parental negativity among SS/SL parents than LL parents. That is, SS/SL parents appeared more susceptible to the effects of disruptive child behavior with respect to their negative parenting. However, genotypes differed significantly only at relatively elevated child noncompliance, suggesting a diathesis-stress relationship where the S allele specifically conferred increased sensitivity to negative environmental conditions (Belsky & Pluess, 2013). Because evaluation of differential susceptibility requires measurement of positive and negative environments, without which true plasticity effects

may be misidentified as diathesis-stress (Belsky & Pluess, 2013), future studies of G × E for parenting must strategically assess positive environmental conditions.

Among SS/SL parents, parental negativity was positively associated with observed child noncompliance and negatively associated with child-related stress, reinforcing their potentially important dissociation. Whereas child noncompliance consisted of intense, short-term, and in vivo exposure to behavior that robustly predicts parental stress (Theule et al., 2013), child-related stress consisted of ongoing, long-term conditions across various qualities of the parent–child relationship (Hammen et al., 1987), which may include negative child behavior in addition to other parent- and child-level factors (e.g., emotional and social deficits). Thus, observed noncompliance and child-related stress likely reflect episodic (i.e., acute) and chronic stress, respectively. Evidence that episodic and chronic stressors may differentially affect psychosocial outcomes (e.g., depression; Hammen et al., 2009) and be governed by separate underlying neurobiological mechanisms (de Kloet, Joëls, & Holsboer, 2005) is relevant to G × E research. Despite potentially important differences, negative environmental influences are often treated singularly or as if they represent a unitary construct. However, plasticity or risk genotypes are likely susceptible to some risk factors or stressors and not others (Belsky & Pluess, 2013), rather than to stress in general, further highlighting the importance of multi-method measurement of differentiated stress constructs in G × E. Inclusion of this approach is thus a unique strength of the present study and a critical priority for future studies on 5-HTTLPR and parenting.

Several study limitations should be considered. First, these cross-sectional data likely reflect reciprocal associations among parenting, child behavior, and parental stress (Hipwell et al., 2008; Neece et al., 2012). Thus, prospective longitudinal designs should be prioritized. Second, although observational measures of parenting have considerable validity, parenting behavior represents a dynamic process in which multiple dimensions are evident simultaneously. For example, parenting characterized as both highly controlling and lacking affection was more predictive of youth depression than parenting configurations consisting of high affection and high control or high affection and low control (Stein et al., 2000). We await studies that identify predictors of configurations of parenting behavior across critical dimensions. Third, although incorporation of multi-method measures of both child-related stress and disruptive child behavior was a strength in this study, the range of scores was somewhat limited. Fourth, despite our use of reliable measures, which maximizes statistical power (Moffitt et al., 2005), the analyses did not survive correction for multiple tests and were limited by the modest sample size. Finally, the challenges inherent to G × E research, including replication failure and false positives (Duncan & Keller, 2011), should be acknowledged, especially given that this study did not employ a built-in replication sample. Given the importance of balancing genetic discovery with costly replication, identification of novel G × E is only an initial step in characterizing and interpreting putative genetic effects. That is, the results described herein require further prosecution, including via experimental and longitudinal designs (van Ijzendoorn & Bakermans-Kranenburg, 2012).

This study evaluated the association of parental 5-HTTLPR with positive and negative dimensions of parenting behavior within the context of uniquely stringent statistical models and found preliminary evidence that 5-HTTLPR (a) is associated with parental praise, (b) interacts with child-related stress to predict parental negativity, and (c) interacts with disruptive child behavior to predict parental negativity. In addition to continued examination of the nature of the association (i.e., positive, negative, interactive) of 5-HTTLPR with multiple dimensions of parenting behavior, it will be important to eventually understand the proximal mechanisms that mediate the direct or interactive effects of this polymorphism on parenting. Crucially, improved identification of high-risk families will logically follow from the establishment of reliable biological determinants of parenting behavior. Likewise, characterization of the causal processes underlying parenting behavior will highlight more precise targets for parenting-based interventions (Luthar et al., 2006), demonstrating how genetic association research may be translated to the promotion of healthy development and resilience in youth.

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